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Histamine in the kidneys: what is its role in renal pathophysiology?

Running Title: Histamine, kidneys and renal disease

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ACR and CG conceived and designed the study; ACR, CG and MG drafted the article; ACR, RF and AP critically revised the article for important intellectual content; MG and RV performed literature searches.

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Nomenclature of Targets and Ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org , the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding et al., 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 (Alexander et al., 2017).

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Conflict of Interest Statement

None

Abstract

Starting from the histamine role in the renal haemodynamic, over time, spare evidence suggested a wider range of action on renal function and renewed the interest on the pathophysiological role of histamine in the kidney. This review intends to provide an up-to-date focus on this topic. According to the intrarenal production of histamine and the renal presence of its receptors, the histaminergic machinery appears to be well suited. The distribution of histamine receptors supports their differential effects but do not exclude the redundancy of H_1 and H_2 receptors in renal haemodynamics, the complementary role of H_1 and H_4 receptors in renal filtration and reabsorption, and the dichotomy between local and neuronal H_1 and H_3 receptors. Experimental models of renal diseases rise the hypothesis of new therapeutic approaches histamine based. A complete elucidation of the influence of the renal regulation by histamine is still ongoing.

Keywords: renal pathophysiology, histamine, histamine receptors, kidneys, renal disease

Abbreviations: alpha-HH = alpha-hydrazinohistidine; AQP = aquaporin; DAO = diaminoxidase; GBM = glomerular basement membrane; GFR = glomerular filtration rate; HDC = histidine decarboxylase; HNMT = histamine-N-methyltransferase; K_f = ultrafiltration coefficient; OCT = organic cation transporter; PA = puromycin aminoglycoside; TGF = transforming growth factor; ZO = zonula occludens

Douglas (1971) wrote *"the core of the matter is that, while the autacoids possess an astonishingly wide range of pharmacological activities [...], there are comparatively few instances where a physiological role can be stated with assurance"*. Compared to its pleiotropic effects, the therapeutic strategies based on histamine targeting are very few: H_1 receptor antihistamines for the treatment of allergy (Simons and Simons, 2011), H_2 receptor antagonists for peptic ulcer (Singh *et al*., 2018) and the H_3 receptor inverse agonist pitolisant for narcolepsy (Kollb-Sielecka *et al*., 2017).

Other effects exerted by histamine cannot be translated to therapeutic approaches till the contribute of the amine to a specific pathophysiological event is not functionally weighed. Therefore, looking at the kidney, the goal is to define the role of the amine in the renal pathophysiology. The evidence for histamine playing a role in this organ has been scanty investigated over the years. In renal plethysmografic studies (Dale and Laidlaw, 1910; Dale and Richards, 1918) histamine injection evoked the renal arteriolar constriction. Renal arteriolar constriction triggers the alteration of the glomerular hydrostatic pressure and causes the reduction of the renal blood flow. These events culminate in the modulation of the glomerular filtration rate (GFR): reduced by renal afferent arteriolar constriction and increased by renal efferent arteriolar constriction (Dalal and Sehdev, 2018). The changes induced by the amine on the renal circulation could account for the drop in both urea and creatinine clearance observed after histamine injections in human subjects with various cardiovascular and renal pathologies (Bjering, 1937). These acute effects were observed after a high loading dose of histamine (1 mg s.c.) and were accompanied by a simultaneous fall in blood pressure, therefore might be due to a systemic vascular event elicited by the amine. However, Bjering (1937) stressed that it is reasonable to assume that histamine affects both the glomerular and tubular function. Indeed, an increase in protein concentration causes the rise of the glomerular capillary oncotic pressure with a consequent decrease in GFR (Dalal and Sehdev, 2018). It was noted that in dogs histamine injection was able to acutely induced albuminuria (1 day after histamine load), and degenerative tubules changes after 7 days (Bjering, 1937). Anyway, since that time, histamine's contribution to renal function was always linked to its vasoactive properties, relegating histamine to the sole role of haemodynamic regulation (Pini *et al*., 2016b). Some time later, between the '70s-'80s, the possibility that histamine played a role in renal immune-mediated diseases was explored, but no conclusive data was provided. In the last decade the discovery of the presence of all the known histamine receptors [$H_{1\text{-}4}$ receptors; as designated by International Union of Pharmacology – IUPHAR; Alexander et al., 2017)] on residential renal cells renewed the interest for the possible role of histamine in renal function. Therefore, this review intends to provide an up-to-date focus on data supporting the possible pathophysiological role of histamine in the mammalian kidney.

The histaminergic machinery in the kidneys

The presence of the histamine metabolic enzymes diaminoxidase (DAO, whose metabolic product is the imidazole-4-acetaldehyde) (Wolvekamp and de Bruin, 1994) and histamine-N-methyltransferase (HNMT, producing the N-methyl-histamine) (Brown *et al*., 1959) in the cytoplasm of renal residential cells highlights that histamine is handled by the kidney, but the source of the amine in this organ has been the subject of some discussion. Histamine enters the intracellular system through active transport by the organic cation transporter (OCT)-2 (Ogasawara *et al*., 2006), expressed exclusively in renal tissue (Aoki *et al*., 2008). However, the hypothesis that histamine in the kidney could derive only from the circulatory system may be retained unlikely. A first observation in keeping with this theory is the ipsilateral histamine synthesis following the infusion of L-histidine, the aminoacid precursor of histamine, into the renal arteries of dogs (Lindell and Schayer, 1958). Nevertheless, the histidine decarboxylase (HDC) enzyme, which is responsible for histamine synthesis, was purified from the kidneys of thyroxine-treated mice in 1986 (Martin and Bishop, 1986). A significant increase in histamine content in the human glomerular suspension was observed when the isolated glomeruli and tubules were incubated with L-histidine 1mM but not with *D*-histidine 1mM, used as negative control. The challenge of isolated glomeruli with the HDC inhibitor brocresine blocked the accumulation of histamine evoked by L-histidine (Sedor and Abboud, 1984). It could be questioned that brocresine is not selective to HDC, being able to inhibit also the nonspecific aromatic L-amino acid decarboxylase (Hakanson and Liedberg, 1972), as well as to affect histamine catabolism (Binder and Sewing, 1973).

However, a demonstration of the presence of specific HDC enzyme in the glomeruli came already from Heald and Hollis (1976) who purified a glomerular enzyme with an apparent Michaelis-Menten constant (*Km*) for histidine of 240 μM and a optimal pH of 6.2 for histidine 10 mM. On the contrary, the nonspecific aromatic L-amino acid decarboxylase has a higher *Km* (100-10 mM) and an optimum pH independent from histidine concentration.

The observation by Sedor and Abboud (1984) was the first clear evidence of the production and presence of histamine in the kidneys despite the absence of mast cells, the professional source of histamine, in human glomeruli (Li *et al*., 2007). Mast cells have been found to be present in very low constitutive number in the whole kidney (Li *et al*., 2007). Despite the number of mast cells, kidneys have been reported to contain a concentration of histamine ranging from about 2 pmol/mg organ weight (5- to 9-week-old mice) to about 5 pmol/mg organ weight (10- to 14-week-old mice) (Zimmermann *et al*., 2011). Notably, these values are comparable with previously reported amounts (Burtin *et al*., 1982; Sedor and Abboud, 1984) and are far above circulating levels in humans (< 10 nM). This content was paralleled by levels of the histamine metabolite, *N*-methylhistamine, in urine (Zimmermann *et al*., 2011). Collectively, this evidence points out the possibility of a local intrarenal production and secretion of histamine. The wide distribution of HDC enzyme other than in mast cells, is now well recognised. It is ubiquitously expressed in the proximal tubules of both mice and humans, both in foetuses and adults (Morgan *et al*., 2006). Notably, the enzyme expression is up-regulated in physiological/adaptive processes. Indeed, HDC is over-expressed in the kidneys of pregnant mice, especially in the superficial cortical zone. These findings suggest that intrarenal produced histamine may increase renal blood flow and recruit superficial cortical nephrons during pregnancy (Morgan *et al*., 2006). However, histamine is also known to exert mitogenic effects, thus potentially contributing to the lengthening of the proximal tubule (Morgan *et al*., 2006).

Whereas the presence of intrarenal produced histamine in the kidneys is now established and documented, which histamine receptor is present and where it is located is still a matter for debate. Indeed, the immunological detection of histamine receptors is biased by antibodies, whose specificity is often questioned. H_1 receptor and H_2 receptor expression on renal vessels has long been established (Banks *et al*., 1978). More recently, an *in vitro* pharmacological approach performed on both primary and immortalised selected renal cell types from different mammals (Table 1), allowed to identified in the nephron and collecting ducts not only the H_1 receptor and H_2 receptor, but also the more recently discovered H_3 receptor and H_4 receptor (Rosa *et al*., 2013; Pini *et al*., 2015; Veglia *et al*., 2015; Veglia *et al*., 2016). A differential distribution of histamine receptors can be observed in the nephron and collecting duct (Figure 1 and Table 1). H_1 receptor is the most prevalent, as it is localised on both the glomerular and tubular levels. It was described in the glomerulus for the first time in 1985, when the H_1 receptor antagonist diphenhydramine (100 μM) suppressed the contractile effects evoked by histamine (5 μM to 100 μM) in a primary culture of mesangial cells from Sprague-Dewley rats (Sedor and Abboud, 1985). Only H_1 receptor and H_2 receptor were known at that time, and the presence of H_2 receptor was demonstrated in the same cells via the measurement of the accumulation of the second messenger cAMP following histamine challenge. The H_2 receptor antagonists cimetidine (Sedor and Abboud, 1985) and metiamide (Torres *et al*., 1978) blunted histamine-induced second messenger production. More recently, a better insight of glomerular histamine receptor presence was provided. Four different cell types can be distinguished within the glomerulus: glomerular endothelial cells, podocytes, mesangial cells and parietal epithelial cells. Podocytes are the most differentiated of these cells and are a crucial component of the glomerular filtration barrier. H_1 receptor expression on human immortalised podocytes was demonstrated by complementary immunohistochemical and pharmacological approaches (Veglia *et al*., 2016). The confocal analysis revealed that in human podocytes only H_1 receptor is localised on the cell membrane. H_1 receptor expression was confirmed by the saturation binding analysis (Veglia *et al*., 2016). Moreover, histamine challenge evoked a sigmoidal dose-dependent increase in IP_3, the second messenger involved in the H_1 receptor singling pathway, but not in cAMP, downstream signal of the histamine receptors (Veglia *et al*., 2016).

The presence of H_1 receptor has also been demonstrated in both the proximal and distal tubules with a similar experimental approach using human primary and immortalised tubular epithelial cells

(TECs) from the renal cortex and the proximal tubular epithelial cell line HK-2 (Veglia *et al*., 2015). This study demonstrated also that H_2 receptor coexists with H_1 receptor in the distal tubules (Veglia *et al*., 2015). Even the H_4 receptor and H_3 receptor subtypes have been found in the kidneys. By immunolabeling and gene expression analyses, the presence of H_4 receptor has been revealed. H_4 receptor shows partial species-dependent distribution (Table 1), with rats expressing it mostly in the ascending limb of Henlé's loop (Rosa *et al*., 2013), and humans and mice mostly on the proximal tubule (Veglia *et al*., 2015; Pini *et al*., 2018). The interspecies variability is in line with previous data on H_4 receptor receptor expression (Liu *et al*., 2001).

The data by immunoassay were confirmed at least in humans by the functional assay evaluating cAMP accumulation following histamine challenge alone or with histamine receptor selective antagonists (Veglia *et al*., 2015). H_3 receptor has surprisingly been found on the principal cells of the collecting duct, both in humans (Veglia *et al*., 2015) and in rats (Pini *et al*., 2015). Again the data were obtained by both immunodetection and gene expression in both *ex-vivo* and *in-vitro* studies (Pini *et al*., 2015; Veglia *et al*., 2015) and were confirmed *in vitro* on human renal cells (Veglia *et al*., 2015), as described above.

The role of histamine in the kidneys

Despite high amount of histamine in kidneys, only few independent data provide evidence of the role that histamine plays in renal haemodynamic and, even less, suggest that it has effects far beyond its vasoactive properties. The data currently available on the role of histamine on renal function do not allow a clear differentiation between the physiological and the pathophysiological effects of histamine and its role in renal diseases. Similarly, is not possible to really discriminate between the effect of the extrarenal and the intrarenal produced histamine. Indeed, the possible role of the amine on kidney function mostly derives from studies in which histamine has been exogenously administered.

Figure 2 summarises the proposed effects of histamine on renal function and the potential contribution of the receptor subtypes. The relative contribution is mostly due to the localisation of the histamine receptors on different renal cell types (Figure 1) and is consistent with the pharmacological characterisation of the histaminergic system in various mammals. Changes in renal circulation have been observed both in normotensive and hypertensive subjects without any history of renal disease challenged with histamine s.c. in the 0.3-0.5 mg range. Both groups showed an elevation in filtration fraction and a reduction in renal plasma flow that were ascribed to the efferent arteriolar constriction, observed in the majority of them (Reubi and Futcher, 1949). On the other side, a higher dose of histamine (1 mg s.c.) caused a fall in blood pressure and a drop in creatinine and urea clearance (Bjering, 1937). It is known that renal blood flow autoregulation is a defensive mechanism that protects the kidney from elevation in arterial pressure and that allows the kidney to maintain a relatively constant GFR (Burke *et al*., 2014). The experimental data are in favour of an active role of at least the extrarenal histamine in regulating GFR, eventually as a possible effector of the renal blood flow autoregulation via H_1 receptor (Banks *et al*., 1984). Indeed, after the intrarenal infusion of chlorpheniramine 10^{-5} mol/min or other H_1 receptor antagonists/inverse agonists, with a variety of chemical structures (terfenadine, diphenhydramine and mepyramine), attenuated the hyperaemia evoked by aortic clamping. Furthermore, a drop in the GFR was measured in parallel (Banks *et al*., 1984). A similar effect was observed when H_1 receptor antagonists were used to counteract histamine infusion-induced renal vasodilation (Banks *et al*., 1978). Interestingly, this study, in accordance with the one by Campbell and Itskovitz (1976) on isolated blood-perfused canine kidneys, failed to demonstrate the involvement of H_2 receptor. However, other reports have published opposing results, in which ranitidine (Laight *et al*., 1995) and cimetidine, but not tripelennamine (Radke *et al*., 1985), blunted histamine-induced vasodilation.

Despite contrasting evidence was provided for the relative contribute of H_1 receptor and H_2 receptor in vasodilation, H_2 receptor has been associated with histamine-induced renin release. Histamine and dimaprit, at that time thought to be an H_2 receptor agonist, induced a significant increase in renin release in dogs, while the H_1 receptor agonist 2-pyridylethylamine had no effect (Gerber and Nies, 1983). Similar conclusions were reached by *ex vivo* studies on isolated perfused rat kidneys. In this model histamine induced renin release in a concentration range 0.5-10 µM, and vasodilation appears only at 100 µM. The H_2 receptor antagonist ranitidine inhibited the renin release induced by histamine. In this study the H_1 receptor agonist 2-pyridylethylamine demonstrated a low stimulatory activity, but only at 10 µM, a dose at which partial H_2 receptor agonism was shown (Schwertschlag and Hackenthal, 1982). cAMP accumulation, evoked by H_2 receptor stimulation in cultured rat mesangial cells (Sedor and Abboud, 1984), was hypothesised to be the underling mechanism. Indeed, any increase in cAMP in renin-secreting cells, such as juxtaglomerular cells, has been reported to stimulates renin secretion (Castrop *et al*., 2010). Therefore, on the basis of the role of the renin-angiotensin-system in vasoconstriction, histamine can contribute to the efferent arteriolar constriction, at least via the H_2 receptor-renin axis.

Due to the role of the sympathetic nerve activity in renal haemodynamic, the noradrenergic transmission was the other mediator of vasoconstriction for which an interplay with histamine has been investigated. The possibility that indirect effects could involve the noradrenergic transmission was discounted after negative results were obtained in an atenolol 1 µM infusion test. However, the histaminergic system may be involved in the regulation of renal noradrenergic neurotransmission, like in the uterus (Montesino *et al*., 1995). Lateral cerebral ventricular injection of histamine in anaesthetised rats demonstrated opposite effects on renal sympathetic nerve activity, in a dose-dependent manner: 100 nM suppressed and 100 mM stimulated the renal sympathetic nerve activity (Tanida *et al*., 2007). These effects suggest that the renal noradrenergic neurotransmission can be affected by the central histaminergic system. H_1 receptor and H_3 receptor were both implicated, with H_1 receptor involved in the high-dose effects of histamine, and the H_3 receptor involved in the low-dose effects, consistently with the differential affinity of the two receptors for the natural ligand [histamine p*k*i reported for H_1 receptor is 4.7 – 5.9 and for H_3 receptor is 7.8 - 8.3 (Alexander *et al*., 2017)]. Nevertheless, in anaesthetised dogs, following renal nerve stimulation (0.5–2.0 Hz) a decrease in urine flow and urinary sodium excretion and an increase in norepinephrine overflow rate were observed. These effects were reduced by intravenous infusion of the H_3 receptor agonist (*R*)-

alpha-methylhistamine (1 µg/kg/min), while the administration of the H_3 receptor antagonist thioperamide (5 µg/kg/min) evoked an antidiuretic effect and increased the norepinephrine overflow rate (Yamasaki *et al*., 2001).

These effects were ascribed to a possible localisation of the H_3 receptor on renal noradrenergic nerve endings. However, data obtained from rats and humans indicated that H_3 receptor are present in the resident epithelial cells of the collecting duct and that they are colocalised with the vasopressin water channel aquaporin (AQP)-2 (Pini *et al*., 2015; Veglia *et al*., 2015). This localisation renews interest in histamine's effect on diuresis. A role for central histamine in regulating diuresis has, in fact, been postulated. Histamine was found to depolarise supraoptic neurons that contain vasopressin, causing vasopressin release from axonal endings in the neurohypophysis (Selbach and Haas, 2008). High doses of histamine (25-500 µg i.c.v.) have been observed to elicit a dose-dependent antidiuretic response with a concomitant rise in blood vasopressin in dogs (Bhargava *et al*., 1973), although tachifilaxis occurred after four doses of histamine 400 µg i.c.v. Mepyramine 5 mg i.c.v. prevented these effects. H_3 receptor had not yet been discovered at the time of this study, and its potential contribution has never been investigated. Nevertheless, its colocalisation with AQP-2 suggests that H_3 receptor and AQP-2 may cooperate in the vasoprssin response of the principal cells in the collecting duct. Although there is evidence for an antidiuretic effect of histamine (Dale and Laidlaw, 1910; Dale and Richards, 1918; Reubi and Futcher, 1949; Blackmore and Cherry, 1955), there is also contrasting evidence to suggest that histamine does not affect urine outflow (Campbell and Itskovitz, 1976), or even increase water excretion (Sinclair *et al*., 1974a; Banks *et al*., 1978; Ichikawa and Brenner, 1979). Similarly, conflicting data also exist on the histamine receptor subtype involved. Banks *et al*. (1978) demonstrated that histamine infusion in dogs (1 µg/min per kg) increased urine outflow; dimaprit produced a similar effect and the 2-pyridylethylamine reduced the urinary flow rate. These data led to the hypotheses that H_2 receptor has an active role in water excretion; however, we must remember that dimaprit is not an H_2 receptor agonist, thought to acts on both H_2 receptor and H_4 receptor (Lim *et al*., 2009), now has been classified as H_3 receptor [p*k*i = 6.1 (Alexander *et* *al.*, 2017)] and H_4 receptor agonist [p*k*i = 4.9 - 6.5 (Alexander *et al.*, 2017)]. *In vivo* experimental models of renal disease with polyuric phenotype, such as diabetic nephropathy, demonstrated that pre-treatment with the H_4 receptor antagonist JNJ-39758979 reduces the urine outflow of diabetic animals in a dose-dependent manner (Pini *et al.*, 2018). Convergent evidence comes from unpublished data demonstrating the involvement of H_4 receptor in the AQPs pattern of expression (Pini, 2018, unpublished data; Verta, 2018, unpublished data). Moreover, the pre-treatment of animals with the H_1 receptor antagonist tripelennamine has been shown to significantly reduce renal responses to histamine infusion, including diuresis (O'Brien and Williamson, 1971). Accordingly, polyuria has been reduced by the administration of (*R*)-cetirizine at 0.5 mg/kg/day in a model of diabetic nephropathy in rats (Anbar *et al.*, 2016).

H_1 receptor was found to be correlated with a decrease in the ultrafiltration coefficient (K_f) induced by histamine (Ichikawa and Brenner, 1979). These data are consistent with the localisation of H_1 receptor on podocytes (Veglia *et al.*, 2016). Interestingly, it has been demonstrated that histamine affects the disruption of cell-to-cell contact, via H_1 receptor activation, in an *in vitro* model of human immortalised podocytes. In particular, histamine was found to downregulate the expression of two key molecular components of the slit diaphragm, zonula occludens (ZO)-1 and P-cadherin, leading to a dose- and time-dependent efflux of albumin. Chlorpheniramine, at 10 µM, was able to restore junctional integrity (Veglia *et al.*, 2016). These data are consistent with the theory that histamine affects the glomerular pore density with a reduction in total filtration surface area (Ichikawa and Brenner, 1979). Nonetheless, histamine i.p. injection at 0.5 mg/kg has been observed to cause foot processes loss in fasting rats (Gurgen *et al.*, 2013). These glomerular changes correlate with the filtration capacity of the kidneys and affect creatinine and urea clearance. In fact, the effect of H_2 receptor antagonists on creatinine clearance has been extensively studied, and cimetidine has been reported to significantly decrease this parameter after 7 days of treatment. This effect is not a class-effect as it was not reported for other H_2 receptor antagonists, such as famotidine (Ishigami *et al.*, 1989), and is therefore histamine-independent. However, *in vivo* models of diabetic nephropathy in mice and rats have demonstrated that both (R)-cetirizine (Anbar *et al*., 2016) and JNJ-39758979 (Pini *et al*., 2018) dramatically restored creatinine clearance in diabetic animals.

Histamine challenge may be directly responsible for the appearance of albuminuria and proteinuria (Bjering, 1937). Interestingly, H_1 receptor antagonism has been reported to reduce the degree of proteinuria in an experimental model of glomerular nephritis (Bolton *et al*., 1974) and in diabetes, where also an amelioration of albuminuria has also been reported (Anbar *et al*., 2016). These effects are consistent not only with the vascular events associated with histamine receptors, but also with the localisation of H_1 receptor on glomeruli, and, more precisely, on podocytes. Indeed, the reduction in filtration area, caused for instance by fenestration and podocyte loss, is a direct contributor to hyper-filtration and the consequent albuminuria (Nagata, 2016). However, glomerular hyper-filtration could be also triggered by hyper-reabsorption at the proximal tubule, through the decreases of electrolyte load to the macula densa, causing an increase in the colloid osmotic pressure of the glomerular capillaries (Palatini, 2012). The proximal tubules, where both H_1 receptor and H_4 receptor (Figure 1) are present, are specialised for albumin and protein reabsorption. In particular, the megalin/cubilin pathway mediates albumin reabsorption. Interestingly, the H_4 receptor antagonist JNJ-39758979 has been found to prevent megalin loss in a model of experimental diabetic nephropathy (Pini *et al*., 2018). The dysregulation of the reabsortive process at the different levels of the nephron may account for the excretion of electrolytes, particularly sodium, excretion induced by histamine via H_1 receptor (Sinclair *et al*., 1974b; Banks *et al*., 1978; Ichikawa and Brenner, 1979; Gerber and Nies, 1983; Laight *et al*., 1995). Furthermore, a potential role for H_4 receptor should be considered, even if it has yet to be investigated.

Despite the evidence of functional effects of histamine in the kidney, the actual relevance of the contribute of this amine cannot be conclusive demonstrated. Currently, the experimental data are in favour of at least an additive role.

Histamine and renal disease

The role of histamine in renal disease can be extrapolated in accordance with the above-reported analysis. Moreover, the relative contribution of each histamine receptor reflects their distribution, with histamine triggering both degenerative glomerular and tubular changes (Bjering, 1937; Gurgen *et al*., 2013), via different histamine receptor pathways.

The correlation between histamine and renal disease in humans comes from the observation that, compared to healthy subjects, plasma levels of histamine are significantly higher in patients that have nephrotic syndrome, end stage renal failure, and undergoing haemodialysis or peritoneal dialysis than in the healthy ones (Gill *et al*., 1991). In particular, high plasma histamine levels have been found in patients with renal insufficiency and uremic pruritus (Stockenhuber *et al*., 1990). This data is consistent with histamine's ability to reduce urea clearance (Bjering, 1937). Histamine may therefore have detrimental effects on renal function. This hypothesis is supported by a number of *in vivo* studies reported in Table 2. However, the role of histamine in renal diseases can also be hypothesised in terms of the presence of mast cells in several kidney diseases with a prominent fibrotic component. Regardless of the underlying disease, the presence of mast cells has been found to correlate with the progressive loss of renal function (Holdsworth and Summers, 2008). An increase in mast cells was found to parallel renal function in primary and secondary forms of membranous, diabetic and IgA nephropathy, and in allograft rejection (Roberts and Brenchley, 2000), as well as in amyloidosis, renovascular ischemia, reflux nephropathy, polycystic kidney disease and drug induced nephropathy (Holdsworth and Summers, 2008). The inhibition of mast cells has also been proposed as a possible target in tubulointestitial fibrosis (Li *et al*., 2007). Mast cells liberate a variety of well-characterized profibrotic mediators, including transforming growth factor (TGF)-ß. Nevertheless, histamine has been shown to induce a profibrotic response via H_4 receptor activation. Indeed, the H_4 receptor antagonist prototype JNJ 7777120 was found to blunt the fibrotic response by down-regulating the TGF-ß-Smad3/4 pathway in a model of pulmonary fibrosis induced by bleomycin, in mice (Rosa *et al*., 2014; Lucarini *et al*., 2016). Moreover, the H_4 receptor antagonist JNJ-39758979 [p*k*i = 7.9 (Alexander *et al*., 2017)] prevented collagen deposition and fibrosis development in the kidneys of diabetic animals (Pini *et al*., 2018). However, Kim *et al*. (2009) hypothesised that mast cells may exert a protective role in renal fibrosis secondary to obstructive uropathy in a mouse model genetically deficient in mast cells.

As shown in Table 2, the majority of the publications are based on streptozotocin-induced type 1 diabetes, which causes long term renal damage, that is consistent with diabetic nephropathy. Results in mice and rats were comparable, indicating that histaminergic tone is higher in diabetic animals than in controls (Markle *et al*., 1986; Gill *et al*., 1988; Gill *et al*., 1990; Rosa *et al*., 2013). In particular, HDC expression has been noted to occur in the tubular and peritubular areas in the diabetic kidney of mice (Pini *et al*., 2018). This evidence is consistent with previous studies reporting an over-activity of HDC. In diabetic rats the increase in renal histamine content was blunted by the administration of the selective HDC inhibitor alpha-hydrazinohistidine (alpha-HH) (Levine *et al*., 1965), but not by insulin (Markle *et al*., 1986). Based on these results, the authors proposed a possible increase in renal HDC activity in diabetic animals. However, being the alpha-HH administered at 25 mg/kg/day i.p. via an intra-abdominally implanted pump, a systemic effect could not be ruled out. The data from Gill *et al*. (1990) supported the hypothesis of an increase in renal HDC activity in diabetes. Indeed, comparing the HDC activity, the histamine content and the DAO activity in different tissue from diabetic rats, the kidney was found to be the second (aorta the first) for HDC activity and histamine levels, with an increase of 70 % over control. Any concomitant decrease in DAO activity was observed in kidney of diabetic animals. All these data are in favour of a net increase in the local synthesis of histamine. Besides an increase in the renal histamine content, some evidence has been provided in favour of a general up-regulation of the histaminergic system in the kidney of diabetic mice. Indeed, the immunolabeling and the gene expression analyses revealed that at least H_4 receptor (Rosa *et al*., 2013) and H_3 receptor (Pini *et al*., 2015) expression is up-regulated in the kidney of diabetic rats. Moreover, preliminary data report that renal H_4 receptor expression parallel the hierarchical susceptibility to diabetic nephropathy induced by streptozotocin injection in different strain of mice (Gurley *et al*., 2006): absent in Balb/c (not susceptible), medium in C57BL/6 and higher in DBA2/J (most susceptible). Also H_1 receptor and H_2 receptor expression was increased in diabetic mice from both C57BL/6 and DBA2/J strain (Pini *et al*., 2016a). However, the functional meaning of these changes is still far to be completely elucidated. Two pharmacological approaches were tested in the streptozotocin-induced diabetic nephropathy model: one was based on H_1 receptor, while the other on H_4 receptor antagonism (Table 2). The two strategies can be considered complementary: H_1 receptor were directed to the glomerulus and H_4 receptor to the tubules, according to their localisation. It is currently thought that the antagonism of H_1 receptor may prevent the integrity of the filtration barrier and reduce the mechanical damage caused by hyperglycaemia, as it is consistent with preserved junctional integrity at the slit diaphragm level (Veglia *et al*., 2016). Nevertheless, the detrimental effect of histamine on the filtration slit is in keeping with previous observations. In particular, Abboud *et al.* (1982), using a model of nephrosis with predominantly direct podocyte damage, the puromycin aminoglycoside (PAN)-induced nephrosis, stated that histamine levels are significantly increased in in the renal cortex of nephrotic rats. Notably, (R)-cetirizine have been demonstrated to reduce the focal segmental glomerulosclerosis, interstitial fibrosis and the thickening of the glomerular basement membrane (GBM) shown by diabetic rats, with a significant improvement in renal function. These changes were accompanied by a reduction in the renal inflammatory response (Anbar *et al*., 2016). On the other hand, in a model of diabetic mice, the H_4 receptor antagonist JNJ-39758979 has been demonstrated to preserve the tubular reabsortive machinery, triggering protective effects on glomerular integrity and a positive outcome on renal function. Once again, a reduction in the renal inflammatory response was observed (Pini *et al*., 2018). The role of histamine in inflammatory and immune response has long been the main subject of evaluation. However, only a few studies have aimed to evaluate histamine's contribution in models of renal diseases with a high immune component (Table 2). Notably, interesting but conflicting evidence has been reported. Two out of three studies on the anti-GBM-induced glomerulonephritis model failed in demonstrate an active role for histamine. However, in the late stage of glomerulonephritis the infiltration by histamine containing cells and, consequently, the histamine levels, in kidney of rats were reduced (Kossi and

Nahas, 2006). Moreover, both diphenhydramine and cimetidine prevented the GFR decrease, without influencing the anti-GBM antibodies ability to induce the glomerular pathological changes (Wilson *et al*., 1981). Therefore, the hypothesis that histamine can trigger the associated fibrotic response was discounted. By contrast, a study by Tanda *et al*. (2007) suggested that H_4 receptor agonism may provide beneficial effects by suppressing the immune response. However, clozapine was used as the H_4 receptor agonist [p*k*i = 6.2 - 6.7 (Alexander *et al*., 2017)] in this study, but this antipsychotic drug binds many other different receptors, H_1 receptor and H_3 receptor included [p*k*i = 8.8 - 9.6 and p*k*i = 5.8 for H_1 receptor and H_3 receptor, respectively (Alexander *et al*., 2017)]. Another study demonstrated that cyproheptadine, blocking H_1 receptor, delayed the onset and reduced the degree of proteinuria (Bolton *et al*., 1974) in a model of autologous immune complex glomerulonephritis, which mimics human membranous glomerulopathy. These effects were, at least partially, ascribed to the vasoactive properties of histamine, but a partial serotonin-depended effect could not be ruled out. The contribute of histamine in renal haemodynamics led to evaluate its role in ischemia-induced acute renal failure. Almost convergent lines of evidence was provided to indicate that beneficial effects can be achieved following an anti-histaminergic approach. Indeed, DAO administration (0.5 U/kg i.v.) inhibited the induced vascular permeability, as well as preserved renal function and structure integrity in a model of ischemia (30 min)/reperfusion (24 h) and in another of unilaterally nephrectomy in rats. The combined administration of diphenhydramine and ranitidine (each at 10 mg/kg) evoked similar effects (Kaneko *et al*., 1998). Nonetheless, the histamine-release inducer compound 48/80 has been demonstrated to worsen kidney injury induced by bilateral renal artery and vein occlusion for 45 min, followed by 24 h of reperfusion. Consistently, a beneficial effect was obtained with the administration of cromoglicic acid (Tong *et al*., 2016). The suggested contribution of H_2 receptor was confirmed by pretreating rats for 7 days with ranitidine 10 mg/kg/day in drinking water before left vascular pedicle clamping for 50 min in uninephrectomised animals. The drug significantly reduced the mortality at day 7 (Vannay *et al*., 2004). However, Kurata *et al*. (2006), obtained contrasting results as they demonstrated the protective effect of carnosine (15 nmol i.v.) 2-weeks after the occlusion of the left renal artery and vein for 45 min. carnosine is a precursor of L-histidine and, consequently, of L-histamine. Notably, the H_3 receptor agonist (R)alpha-methylhistamine (5 pmol i.c.v.) mimicked the effects of carnosine, while the use of the H_3 receptor antagonist thioperamide (30 nmol i.c.v.) abolished them (Kurata *et al*., 2006). The influence of H_3 receptor activation in the central nervous system on the observed effects therefore suggests that a dichotomy may exist between peripheral and central histamine in the pathogenesis of ischemic renal failure.

Conclusion

In conclusion, looking at the histaminergic machinery in the kidney, it can be stated that histamine can act on this organ in an autocrine manner under physiological conditions, and in both an autocrine and paracrine manners in pathological conditions, in which either the renal inducible pool of histamine, or an extrarenal source, like mast cells, could occur. The presence of all four histamine receptors, with differential distribution, suggests and further confirms the multiple actions that histamine presents, but may also hint at possible histamine receptor redundancy. The overall data reported in the literature raise the intriguing hypothesis of redundancy between H_1 receptor and H_2 receptor in renal haemodynamics; both mediating the increase in renal blood flow and reducing vascular resistance (Banks *et al*., 1978; Banks *et al*., 1984; Laight *et al*., 1995). Moreover, both H_1 receptor and H_4 receptor have been demonstrated to participate in the complex process of urine formation, with H_1 receptor mostly being involved in glomerular filtration (Anbar *et al*., 2016; Veglia *et al*., 2016) and H_4 receptor in tubular reabsorption (Pini *et al*., 2018). These two receptors therefore appear to possess complementary function(s). However, data from the peripheral and central activation of the histaminergic system, H_1 receptor and H_3 receptor seem to present a dichotomy. The effect of histamine on vasopressin regulation (Bhargava *et al*., 1973; Selbach and Haas, 2008) against increases in water excretion (Sinclair *et al*., 1974a; Banks *et al*., 1978; Ichikawa and Brenner, 1979), as well as targeting at either peripheral or central histamine in ischemic acute renal failure, are examples of this issue. These considerations should be taken into account when exploring possible therapeutic strategies for renal disease.

Preclinical studies of renal injury models point out at the intriguing hypothesis of new therapeutic approaches directed to the histaminergic modulation in kidney diseases. However, the functional influence of histamine in kidney pathophysiology still needs to be completely elucidated before experimental data can be translated to therapeutic applications.

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Figure legends

Figure 1. Differential histamine receptor distribution in the mammalian nephron and collecting duct.

Histamine receptors topology within the mammalian kidney based on current knowledge (Sedor and Abboud, 1984; Sedor and Abboud, 1985; Rosa *et al.*, 2013; Pini *et al.*, 2015; Veglia *et al.*, 2015; Veglia *et al.*, 2016). H_1 receptor and H_2 receptor have been identified within the renal corpuscle (H_1 receptor in the glomerulus and H_2 receptor in glomerulus and in glomerular capsule) and in the distal tubule. H_1 receptor and H_4 receptor are both present on the renal proximal convoluted tubule. H_4 receptor is also expressed in the ascending limb of the loop of Henlé. H_3 receptor have been localised in the collecting duct.

Figure 2. Histamine and histamine receptor contribution to renal function.

Proposed summary of the data reported on the effects of histamine on renal function. The amine mediates a range of effects through the differential contribution of all the histamine receptors. The increases in albuminuria, and water and salt excretion, as well as the reductions in creatinine and urea clearance are mediated by both H_1 receptor and H_4 receptor. Moreover, H_1 receptor also participate in the reduction of the ultrafiltration coefficient as well as the modulation of renal blood flow and vascular resistance. The vasoactive properties of H_1 receptor are shared by H_2 receptor, whose activation also evokes renin release. The role of H_2 receptor in the distal tubule is still unknown. Finally, H_3 receptor activation may be involved in polyuria.